Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Travel Medicine and Infectious Disease 53 (2023) 102565

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Effectiveness of the BBIBP-CorV vaccine in preventing infection and death in health care workers in Peru 2021

Javier Silva-Valencia [a,1], Percy Soto-Becerra [b,c,1], Stefan Escobar-Agreda [a], Manuel Fernandez-Navarro [a], Miguel Moscoso-Porras [a,b], Lely Solari [a,*], Percy Mayta-Tristán [d]

[a] Instituto Nacional de Salud (INS), Jr. Capac Yupanqui 1400, Jesus Maria, Lima, Peru
[b] Universidad Continental, Av San Carlos 1980, Huancayo, 12000, Peru
[c] Seguro Social en Salud (EsSalud), Instituto de Evaluación de Tecnologías Sanitarias e Investigación – IETSI, EsSalud, Domingo Cueto 109, Jesus Maria, Lima, Peru
[d] Universidad Científica del Sur, Dirección General de Investigación, Desarrollo e Innovación, Antigua panamericana Sur Km19, Lima, Peru

ARTICLE INFO

Keywords:
Effectiveness
Health care workers
BBIBP-CorV
Peru

ABSTRACT

Background: During 2021, Peru started the vaccination against SARS-CoV-2 using the BBIBP-CorV inactivated virus vaccine for health care workers (HCW). We aim to evaluate the effectiveness of the BBIBP-CorV vaccine to prevent SARS-CoV-2 infection and deaths among HCWs.
Methods: Retrospective cohort study, from February 9 to June 30, 2021, using national registries of health care workers, laboratory tests for SARS-CoV-2 and deaths. We calculated the vaccine effectiveness for preventing laboratory-confirmed SARS-CoV-2 infection, COVID-19-mortality, and all-cause mortality among partially immunized and fully immunized HCWs. An extension of Cox proportional hazards regression was used to model the mortality results, and Poisson regression was used to model SARS-CoV-2 infection.
Results: The study included 606,772 eligible HCWs, the mean age was 40 (IQR: 33.0, 51.0). In fully immunized HCW, the effectiveness for preventing all-cause mortality was 83.6 (95% CI: 80.2 to 86.4), 88.7 (95% CI: 85.1 to 91.4) for preventing COVID-19 mortality, and 40.3 (95% CI 38.9 to 41.6) for preventing SARS-CoV-2 infection.
Conclusion: The BBIBP-CorV vaccine showed high levels of effectiveness for preventing all-cause and COVID-19 deaths among fully immunized HCW. These results were consistent within different subgroups and sensitivity analyses. However, the effectiveness for preventing infection was suboptimal in this particular setting.

1. Introduction

Vaccines are the most important tool to prevent severe disease and mortality caused by SARS-CoV-2. By December 2021, there were more than 140 vaccines under clinical development, and 10 had already been approved by the World Health Organization (WHO) [1]. Latin American countries, including Peru, began vaccinating priority groups since the first trimester of 2021. Vaccines were not available prior to this period due to unequal global distribution and vaccine shortages mostly in low-middle income countries in the global south [2].

The BBIBP-CorV vaccine is an inactivated virus vaccine produced by Sinopharm (China) [3,4]. Its efficacy was initially evaluated in the United Arab Emirates, Bahrain, Egypt and Jordan, and according to the publication of the phase 3 randomized clinical trial, it was 78.1% effective for preventing infection [5]. A test-negative design performed in Bahrain reported vaccine effectiveness for preventing infection of 90% and 91% for adults aged 18–59 and 60 years or older, respectively [6]. On the other hand, Argentina reported 84% effectiveness for preventing deaths in people over 60 years during the first semester of 2021 [7]. Of note, most available evidence on the effectiveness of the BBIBP-CorV vaccine is limited to non-peer reviewed publications such as institutional reports. More scientific studies such as test-negative designs, cohort studies and case control studies are needed and have been recommended by WHO to report COVID-19 vaccine effectiveness. After these initial reports of high efficacy, subsequent observational studies have found low immunogenicity of BBIBP-CorV as assessed by neutralizing antibodies [8,9] and clinical efficacy [10], particularly in the context of the circulation of variants with mutations that confer immune evasion [11].

Peru has been one of the countries with the highest death tolls due to

* Corresponding author. Instituto Nacional de Salud (INS), Centro Nacional de Salud Pública, Jr. Capac Yupanqui 1400, Jesus Maria, Lima, 15073, Peru.
E-mail address: lsolari@ins.gob.pe (L. Solari).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.tmaid.2023.102565
Received 7 November 2022; Received in revised form 3 January 2023; Accepted 9 March 2023
Available online 16 March 2023

COVID-19 [12] and with very high infection rates, as evidenced by high seroprevalence throughout the pandemic [13] being Health Care Workers (HCW) one of the most affected groups with respect to mortality and infection [14]. Vaccine deployment began in February 2021 [15] with the application of the BBIBP-CorV vaccine to HCW during a highly lethal second wave of infection, in which the lambda variant predominated in the coast and Andean regions the country and the gamma variant prevailed in the Amazon basin [16]. This study aims to report the evaluation of the effectiveness of the BBIBP-CorV vaccine in preventing infection, COVID-19 related mortality, and all-cause mortality for among HCW in Peru.

2. Methods

2.1. Study design and population

We conducted a retrospective cohort study to assess the effectiveness of the BBIBP-CorV vaccine in preventing COVID-19 infection and mortality as well as all-cause mortality among Peruvian HCW from February 9 (start of vaccination campaigns in Peru) to June 30, 2021.

The study population consisted of the HCW included in the National Registry of human resources a living census of all HCW in the country (active and retired from the public and private health services), which was assembled by the Ministry of Health (MoH) for the vaccination campaign. Figure A7 shows the diagram of how the National Registry of human resources was constructed. HCW were defined as all personnel involved in direct or indirect patient care or supporting the functioning of the health system. These individuals were categorized as (1) Physicians, (2) Nurses, (3) Other health personnel in direct contact with COVID-19 patients (technicians, midwifes, psychologists), (4) Health professionals with limited contact with COVID-19 patients (nutritionists, pharmacists), and (5) Support and administrative personnel (insurance clerks, logisticians of health facilities). A detailed description of the census and the vaccination campaign in Perú is provided in the Supplementary Appendix (A1-A2). The aforementioned census contains basic demographic and occupational information on each HCW and the date of administration of the first and second doses of the BBIPB-Cor-V vaccine. The BBIPB-Cor-V vaccine used in Peru is the inactivated vaccine (Vero CeI) in injectable suspension from the manufacturer Beijing Institute of Biological Products Co. Ltd of China, which was applied in doses of 0.5 mL intramuscularly, preferably in the upper arm [17].

We excluded participants under 18 and over 100 years old, those who died before the study period and those reporting pregnancy. Although some participants had missing data on demographic variables, they were still included in the analysis. We classified immunization status into three groups: Not immunized (i.e. had not received any dose of vaccine or were less than 14 days since the person received the first dose), partially immunized (i.e. had more than or equal to 14 days after the first dose or less than 14 days after the second dose), and fully immunized (i.e. had more than or equal to 14 days after the second dose).

2.2. Outcomes and covariates

We have three primary outcomes: 1. Laboratory-confirmed SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (RT-PCR) or Antigen Test, 2. COVID-19 related mortality, and 3. All-cause mortality. For these outcomes, we calculated the time from the beginning of follow-up (February 9, 2021) to the occurrence of the event of interest as the endpoint. SARS-CoV-2 infection data was extracted from the National Integrated System for COVID-19 (SICOVID) and the National Laboratory System (NetLab) [18]. During these months, most testing was done on symptomatic cases, rather than on asymptomatic contacts. A detailed description of the health information system is given in the Supplementary Appendix (A2.1).

The data for all-cause mortality and for COVID-19 related mortality were obtained from the death registry of the National Electronic Death Registry (SINADEF, acronym in Spanish). To identify COVID-19 related mortality, we used the following ICD-10 codes: U07.1, U07.2, B34.2, B97.2, or at least one of the following terms: “coronavirus”, “cov-2″, “cov2″, “covid” and “sars".

We adjusted our effectiveness estimates controlling for the following potentially confounding variables [19]: age group, sex, region of residence, occupational group, laboratory confirmed history of SARS-CoV-2 infection prior to the start of follow-up (February 9, 2021), and for the following underlying conditions associated with severe COVID-19: obesity, chronic pulmonary disease, diabetes mellitus, hypertension, cancer, any immunosuppressive condition, asthma, cerebrovascular disease, and chronic kidney failure. The Supplementary Appendix (Table A3) shows the source of data for each variable included in the study.

We integrated data using a deterministic record linkage of each individual. We excluded inconsistent values, and very extreme values on all variables.

2.3. Statistical analysis

We modeled mortality outcomes (all-cause and COVID-19) using the extension of the Cox proportional-hazards regression on a calendar time axis, which allows time-varying immunization status of the subjects in the study. We performed the estimation using the partial maximum likelihood with Breslow correction for ties. We calculated the hazard rate ratios (HRR) according to the immunization status. We performed the analysis for all HCWs included in the study and for HCWs $\geq$60 years separately.

The outcome of SARS-CoV-2 infection was modeled using a Poisson regression with the period (in days) as an exposure to estimate the incidence density ratios (IDR) associated with partial and full immunization. In all cases, adjustment for the potentially confounding variables was performed. Complete case analysis was reported; however, since at least one potentially confounding factor was missing in 34.3% of individuals, we performed an additional analysis using multiple imputation by chained equations (MICE) to reduce bias [20]. Summary of modeling, assumption assessment and imputation are shown in the Supplementary Appendix (A2 Methods). Vaccine effectiveness was estimated as 1 minus the HRR or IRR expressed as a percentage.

As an additional analysis, we performed an interaction term between age group (18–59 years vs. $\geq$ 60 years) and immunization status, and macroregion and immunization status using a hypothesis testing approach to assess differences in effectiveness. In addition, to explore the robustness of our results against potential selection bias, we performed sensitivity analysis to estimate the HRRs and IDR in subjects with and without history of laboratory-confirmed SARS-CoV-2 infection prior to vaccination. Finally, an additional sensitivity analysis was done using vaccination status rather than the immunization status, taking the day of vaccination, and not 14 days after, as the beginning of the protected period. (see Appendix section A3 for additional results and sensitivity analysis).

Sections A2.2 and A2.3 of the Supplementary Appendix detail the study’s statistical methodology. We calculated 95% confidence intervals (95% CI) and p-values with a significance level of 0.05, based on the Wald statistic. We used Stata/SE software, version 17.0 for the creation of the dataset, cleaning, multiple imputation, and Cox regression. Likewise, R software version 4.0.3, was used to generated some reproducible descriptive tables.

2.4. Role of the funding source

This study was approved by the Research Ethics Committee of the Peruvian National Institute of Health (INS Peru), (ID: 10812-2021). Authorization was granted from the MoH and the INS Peru to access the databases. The INS Peru provided finantial support for the study.

The Peruvian MoH, through the INS Peru, conducted the study. All members of the study team were fully responsible of the design of the study, the retrieval and analysis of the data, and for writing the manuscript. All the authors vouch for the accuracy and completeness of the data reported.

3. Results

Of the 606,870 HCW that were vaccinated according to the MoH vaccination registry, 606,772 were eligible according to the inclusion criteria. At the end of the follow-up period, 139,097 (22.9%) had not received any dose of the BBIBP-CorV vaccine, 56,597 (9.3%) had received only one dose, and 411,078 (67.8%) HCW had received two doses of the vaccine (Fig. 1).

Regarding to the characteristics of the participants, during the study period, 26,297 (17.8%) HCW developed a SARS-CoV-2 laboratory confirmed infection, (positive antigen test or RT-PCR), and 1265 died (0.21%), of which 841 (0.13%) were deaths due to COVID-19. Most of the participants were women (66%), with a median age of 40 years (interquartile range [IQR]: 33 to 51), 9.1% had a comorbidity related to COVID-19 such as obesity (3%), diabetes (1.6%) high blood pressure (2.5%), cardiovascular disease (0.9%), asthma or chronic pulmonary disease (6.2%), or other conditions such as immunodeficiency, cancer or chronic renal failure (0.5%). Almost half, 47.1% came from Lima-Callao (capital of Peru), 11.7% were physicians, and 23.9% had a previous history of SARS-CoV-2 infection (Table 1). Detailed information about the HCW category and region of provenance is shown in Table A1.

We performed an analysis in the overall population using two approaches: case-complete and multiple imputation. For the analysis using multiple imputation, we estimated an adjusted vaccine effectiveness in fully immunized HCW of 83.6% (95% CI 80.2%–86.4%) for preventing all-cause mortality, 88.7% (95% CI 85.1%–91.4%) for preventing COVID-19 mortality and 40.3 (95% CI 38.9%–41.6%)) for preventing SARS-CoV-2 infection. Analysis using the case-complete approach showed slightly higher effectiveness values for all outcomes (Table 2).

Fig. 2 shows the cumulative incidence of death in HCW during the study period with respect to all-cause mortality (Fig. 2A) and COVID-19 related mortality (Fig. 2B), and the difference between the fully immunized, partially immunized, and not immunized with respect to adjusted cumulative incidence curves.

Among the HCW ≥60 years: we found an adjusted vaccine effectiveness in fully immunized HCW of 79.2% (95% CI 73.7%–83.6%) for preventing all-cause mortality, 83.4% (95% CI 76.8%–88.1%) for preventing COVID-19 mortality and 45.9% (95% CI 41.8%–49.8%) for preventing SARS-CoV-2 infection. In Table A5 we performed an assessment of effect modification of vaccine effectiveness by age group (18–59 years vs. ≥ 60 years), finding statistical evidence for a higher vaccine effectiveness for full immunization in HCW of 18–59 years in comparison with 60+ years for all-cause mortality (86.4% vs. 79.2%, multiple interaction p-value = 0.014) and COVID-19 mortality (93.3 vs. 83.4%, multiple interaction p-value = 0.002) (Table 3).

Regarding heterogeneity of vaccine effectiveness by macro-region, we found no statistical evidence of effect modification (multiple interaction p-values between 0.7 and 0.9) for all-cause mortality and mortality from COVID-19. Conversely, we did find evidence of effect modification for the outcome of laboratory-confirmed COVID-19 infection (multiple interaction p-value <0.001) (Table A6).

In addition, considering the potential influence of prior infection on vaccine effectiveness, we performed additional sensitivity analysis only in HCW without previous SARS-CoV-2 infection (Table A8). The adjusted vaccine effectiveness using the complete-case data approach in fully immunized HCW was 90.6% (95% CI 87.3%–93.0%) for preventing all-cause mortality, 93.4% (95% CI 89.9%–95.6%), for preventing COVID-19 mortality, and 50% (95% CI 48.6%–51.2%) for preventing SARS-CoV-2 infection.

Finally, considering the potential effectiveness of the vaccine prior to the 14 days after the application of each dose, we performed analyses according to the number of vaccine doses received. The results showed an adjusted effectiveness among those who received two doses of the vaccine of 93.3% (95% CI 91.4%–94.8%) for preventing all-cause mortality, 96.1% (95% CI 94.4%–97.4%), for preventing COVID-19 mortality, and 47.6% (95% CI 46.3%–48.9%) for preventing SARSoV-2 infection (Table A9).

4. Discussion

Our study provides real-world evidence on the effectiveness of the BBIBP-CorV vaccine for the prevention of SARS-CoV-2 infection, all-cause mortality, and COVID-19 mortality in Peruvian HCW during a highly lethal second wave of COVID-19. Peru is considered one of the countries with the highest excess mortality during the pandemic, in particular during this second wave of contagions, in which variants with high infectivity rates and immune escape mechanisms circulated, such as lambda and gamma [21,22]. Using data from national health and administrative registries implemented for the vaccination campaign, we found that the BBIBP-CorV vaccine was 83.6% effective for preventing all-cause mortality, 88.7% effective in preventing COVID-19 related mortality 14 days after the second dose, and 40.3% for preventing

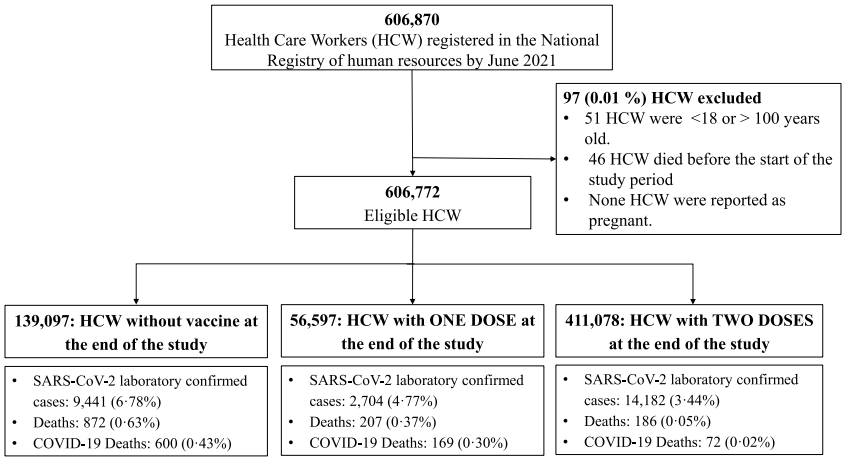

Fig. 1. Health care workers included and number of vaccine doses received.

Table 1
Characteristics of the included health care workers, Peru 2021.

Characteristics	Total (N = 606,772) n (%)(+)	Vaccination Status			Outcomes		
		Unvaccinated (N = 139,097) n (%)(+)	One dose (N = 56,597) n (%)(+)	Two doses (N = 411,078) n (%)(+)	Laboratory-confirmed SARS-CoV-2 infection (N = 26,297) n (%)(+)	All-cause mortality (N = 1265) n (%)(+)	COVID-19 mortality (N = 841) n (%)(+)
Age, median years (IQR)	40 (33·0, 51·0)	41 (32·0, 54·0)	37 (31·0, 46·0)	41 (33·0, 52·0)	39 (32·0, 50·0)	61 (51·0, 68·0)	61.0 (52.0, 67.0)
Missing data[a]	338	328	1	9	0	0	0
Sex							
Female	396,440 (66%)	90,974 (68.1%)	38,880 (68.8%)	266,586 (64.9%)	17,294 (4·4%)	479 (0·1%)	300 (0.1%)
Male	204,539 (34%)	42,658 (31.9%)	17,630 (31.2%)	144,251 (35.1%)	9003 (4·4%)	725 (0·4%)	499 (0.2%)
Missing data[a]	5793	5465	87	241	0	61	42
Age group							
18-29	87,416 (14·4%)	20,708 (14.9%)	9523 (16.8%)	57,185 (13.9%)	3857 (4·4%)	20 (0.x%)	6 (0.0%)
30-39	199,381 (32·9%)	44,295 (31.9%)	23,556 (41.6%)	131,530 (32.0%)	9319 (4·7%)	86 (0.x%)	45 (0.0%)
40-49	145,261 (24%)	30,014 (21.6%)	13,850 (24.5%)	101,397 (24.7%)	6346 (4·4%)	169 (0·1%)	116 (0.1%)
50-59	94,989 (15·7%)	18,871 (13.6%)	6785 (12.0%)	69,333 (16.9%)	3888 (4·1%)	297 (0·3%)	224 (0.2%)
60–80+	79,387 (13·1%)	24,881 (17.9%)	2882 (5.1%)	51,624 (12.6%)	2887 (3·6%)	693 (0·9%)	450 (0.6%)
Missing data[a]	338	328	1	9	0	0	0
Obesity							
No	425,154 (97%)	72,210 (97.9%)	37,307 (97.2%)	315,637 (96.8%)	23,315 (5·5%)	799 (0·2%)	539 (0.1%)
Yes	13,163 (3%)	1526 (2.1%)	1068 (2.8%)	10,569 (3.2%)	1055 (8.x%)	58 (0·4%)	48 (0.4%)
Missing data[a]	168,455	65,361	18,222	84,872	1927	408	254
Diabetes							
No	431,285 (98·4%)	72,597 (98.5%)	37,924 (98.8%)	320,764 (98.3%)	23,826 (5·5%)	783 (0·2%)	535 (0.1%)
Yes	07,032 (1·6%)	1139 (1.5%)	451 (1.2%)	5442 (1.7%)	544 (7·7%)	74 (1·1%)	52 (0.7%)
Missing data[a]	168,455	65,361	18,222	84,872	1927	408	254
High Blood Pressure							
No	427,436 (97·5%)	71,924 (97.5%)	37,690 (98.2%)	317,822 (97.4%)	23,638 (5·5%)	787 (0·2%)	533 (0.1%)
Yes	10,881 (2·5%)	1812 (2.5%)	685 (1.8%)	8384 (2.6%)	732 (6·7%)	70 (0·6%)	54 (0.5%)
Missing data[a]	168,455	65,361	18,222	84,872	1927	408	254
Cardiovascular disease							
No	434,587 (99·1%)	73,202 (99.3%)	38,161 (99.4%)	323,224 (99.1%)	24,064 (5·5%)	832 (0·2%)	569 (0.1%)
Yes	03,730 (0·9%)	534 (0.7%)	214 (0.6%)	2982 (0.9%)	306 (8·2%)	25 (0·7%)	18 (0.5%)
Missing data[a]	168,455	65,361	18,222	84,872	1927	408	254
Asthma or chronic pulmonary disease†							
No	427,562 (97·5%)	72,270 (98.0%)	37,457 (97.6%)	317,835 (97.4%)	23,708 (5·5%)	830 (0·2%)	571 (0.1%)
Yes	10,755 (2·5%)	1466 (2.0%)	918 (2.4%)	8371 (2.6%)	662 (6·2%)	27 (0·3%)	16 (0.1%)
Missing data[a]	168,455	65,361	18,222	84,872	1927	408	254
Immunodeficiency/Cancer/CRF							
No	436,201 (99·5%)	73,271 (99.4%)	38,196 (99.5%)	324,734 (99.5%)	24,217 (5·6%)	817 (0·2%)	577 (0.1%)
Yes	02,116 (0·5%)	465 (0.6%)	179 (0.5%)	1472 (0.5%)	153 (7·2%)	40 (1·9%)	10 (0.5%)
Missing data[a]	168,455	65,361	18,222	84,872	1927	408	254
Previous SARS-CoV-2 infection							
No	461,956 (76·1%)	117,208 (84.3%)	44,424 (78.5%)	300,324 (73.1%)	23,385 (5·1%)	1052 (0·2%)	700 (0.2%)
Yes	144,816 (23·9%)	21,889 (15.7%)	12,173 (21.5%)	110,754 (26.9%)	2912 (2.x%)	213 (0·1%)	141 (0.1%)
Macro-region							
Center	69,954 (12·5%)	9416 (10.3%)	5139 (9.1%)	55,399 (13.5%)	2758 (3·9%)	117 (0·2%)	85 (0.1%)
Lima-Callao	263,225 (47·1%)	44,040 (48.1%)	27,785 (49.1%)	191,400 (46.6%)	12,029 (4·6%)	588 (0·2%)	414 (0.2%)
North	103,862 (18·6%)	16,361 (17.9%)	11,214 (19.8%)	76,287 (18.6%)	4988 (4·8%)	179 (0·2%)	113 (0.1%)
East	38,337 (6·9%)	6004 (6.6%)	2278 (4.0%)	30,055 (7.3%)	2357 (6·1%)	51 (0·1%)	33 (0.1%)
South	83,849 (15%)	15,731 (17.2%)	10,181 (18.0%)	57,937 (14.1%)	4054 (4·8%)	124 (0·1%)	77 (0.1%)
Missing data[a]	47,545	47,545	0	0	111	206	119
Categorized occupation							
Physicians	60,568 (11·7%)	21,098 (20.2%)	6512 (13.7%)	15,805 (4.3%)	2809 (4·6%)	160 (0·3%)	75 (0.2%)
Nurses		13,014 (12.5%)	5230 (11.0%)	59,306 (16.1%)	3620 (4·7%)	100 (0·1%)	65 (0.1%)

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Total (N = 606,772) n (%)(+)	Vaccination Status			Outcomes		
		Unvaccinated (N = 139,097) n (%)(+)	One dose (N = 56,597) n (%)(+)	Two doses (N = 411,078) n (%)(+)	Laboratory-confirmed SARS-CoV-2 infection (N = 26,297) n (%)(+)	All-cause mortality (N = 1265) n (%)(+)	COVID-19 mortality (N = 841) n (%)(+)
	77,550 (14·9%)						
Other Health personnel in direct contact with patients	222,412 (42·8%)	5657 (5.4%)	4048 (8.5%)	50,863 (13.8%)	9749 (4·4%)	322 (0·1%)	109 (0.2%)
Health personnel not in direct contact with patients	43,415 (8·4%)	41,704 (40.0%)	23,942 (50.5%)	156,766 (42.6%)	1940 (4·5%)	106 (0·2%)	222 (0.1%)
Administrative personnel	115,582 (22·2%)	22,866 (21.9%)	7705 (16.2%)	85,011 (23.1%)	5240 (4·5%)	196 (0·2%)	137 (0.1%)
Missing data[a]	87,245	34,758	9160	43,327	2939	381	233

IQR: interquartile range; CRF: Chronic renal failure; (+): Column percentage; (+) Row percentage.
All comorbidities (obesity, diabetes, high blood pressure, asthma or chronic pulmonary disease, Immunodeficiency/Cancer/CRF) where auto reported data.
[a] Missing data were not considered for calculation of Col% and Row%.

Table 2
Effectiveness of BBIBP-CorV vaccine in health care workers for all-cause mortality, COVID-19 mortality, and SARS-CoV-2 infection.

Outcomes	Person-days at risk	Outcome events	Outcome rate per 100,000 person-days[a]	Vaccine effectiveness[b] (95% CI)	
				Complete case analysis	Analysis with multiple imputation
All-cause Mortality					
Not immunized	37,268,955	872	2·34	..	..
Partially immunized	12,276,194	199	1·62	50·8 (38·2 to 60·9)	42·4 (31·9 to 51·3)
Fully immunized	35,239,437	170	0·48	90·5 (87·7 to 92·7)	83·6 (80·2 to 86·4)
COVID-19 Mortality					
Not immunized	37,268,955	600	1·61	..	..
Partially immunized	12,276,194	156	1·27	45·2 (28·8 to 57·8)	34·3 (20·3 to 45·9)
Fully immunized	35,239,437	66	0·19	93·9 (90·9 to 95·9)	88·7 (85·1 to 91·4)
SARS-CoV-2 infection					
Not immunized	37,268,955	20,261	54·36	..	..
Partially immunized	12,276,194	6858	55·86	15·3 (12·7 to 17·8)	−0·1 (−2·9 to 2·6)
Fully immunized	35,239,437	11,580	32·86	49·2 (47·9 to 50·4)	40·3 (38·9 to 41·6)

95% CI: 95% confidence interval.
[a] Outcome rate calculated for case complete analysis.
[b] Analyses adjusted for sex, age group, macro-region, occupation, previous infection and the presence of obesity, diabetes, high blood pressure, cardiovascular disease, asthma or chronic pulmonary disease, and immunodeficiency or cancer.

SARS-CoV-2 infection in HCW. All of these effectiveness estimates were robust in the multiple sensitivity analyses that we performed.

Overall, our results indicate that the BBIBP-CorV vaccine had a high effectiveness for saving lives during the second wave of contagion. Our estimate of vaccine effectiveness in preventing COVID-19 mortality is similar to estimates reached in Argentina for the elderly (80.2% 95% CI 67.5–88.4 for ages 60–69 and 88.3% 95% CI 80.1–93.1 for ages 70–79) [7], but lower than the reported in the phase 3 randomized clinical trial published by Al Kaabi [5], which attained 100% vaccine efficacy for death prevention. This was expected, as estimates of effectiveness are usually lower than those of efficacy. Other considerations, such as differences in local transmission dynamics, circulating variants, and the prevalence of risk factors like obesity, hypertension and diabetes in our population could further contribute to the differences in the results. We would like to stress the fact that this study was performed in the middle of a highly lethal second wave of contagions of COVID-19, in which the lambda variant predominated in the coast and highlands and the gamma variant in the amazon basin of Peru, so these results are not necessarily generalizable to other contexts with other circulating SARS-CoV-2 variants.

Concerning infection, our estimates of vaccine effectiveness to prevent SARS-CoV-2 infection were lower than those reported in the clinical trial from Bahrain (78.1%. 95% CI, 64.8%–86.3%) [5] and lower than those estimated by a group of experts of the WHO (90%. 95% CI, 88%–91%).[6] This was unexpected, most of all considering that most of the reported infections were symptomatic episodes. Of note, Peruvian HCWs have much more access to diagnostic tests for COVID-19 than other groups [23]. Moreover, apart from inherent failure for preventing infection due to intrinsic characteristics of this vaccine, an alternative explanation for the low estimated effectiveness could be the presence of the "Peltzmann effect" which suggests that the adoption of risk behaviors increases in vaccinated people [24]. In addition, HCWs are a group with a particularly high exposure to infection in compared to the general population as in Bahrain.

Although head-to-head comparisons were not reported, experience at the global level shows that the efficacy and effectiveness of inactivated virus vaccines to prevent SARS-COV-2 related outcomes are lower in comparison to viral vector and mostly to mRNA-based vaccines [25]. This could be the case, particularly for infection, as our estimates of effectiveness were lower than those reported with the mRNA vaccines in Israel [25], and the USA [26]. Besides factors inherent to the vaccine type, issues related to the collapse of the health systems and the circulating variants (lambda and gamma) may have played a role in determining these differences. Moreover, since then, the phenomenon of the loss of effectiveness of vaccines against subsequent viral variants has been found with all available vaccines, driving the countries to the need of applying booster doses [26]. Indeed, an important issue to address in the coming months is how the different mixtures of vaccines will provide protection against the emerging variants like Omicron or eventually, the new strains of the virus.

In low-and-middle-income countries, there are some other aspects besides efficacy and effectiveness that should be considered in the

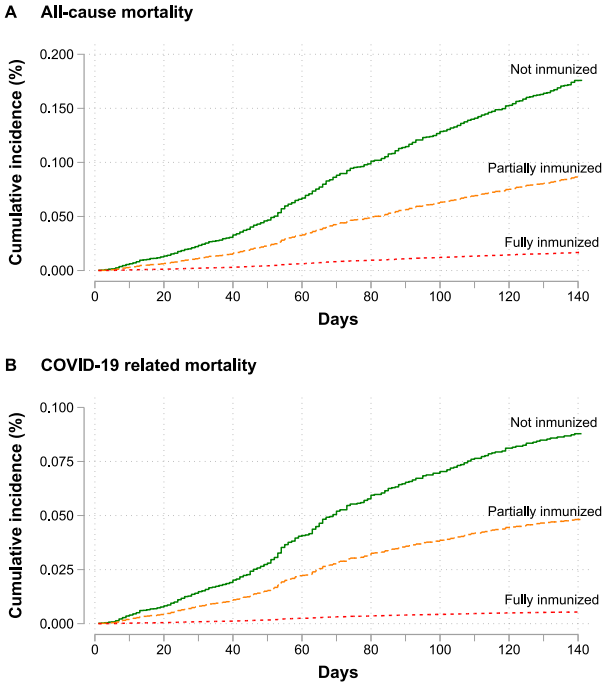

Fig. 2. All-cause and COVID-19 related mortality in health care workers according to immunization status.

implementation of vaccination programs. The mRNA vaccines were not available for many Latin-American countries during the first few months after their approval, and were only deployed in North America, Europe, and some other selected countries. In this scenario, our study shows that timely implementation of available technologies, such as the BBIBP-CorV an inactivated virus vaccine, represented an excellent opportunity to save the lives of those at highest risk. Access to health care is centralized in Peru and most resources, including ultra-freezers required by the mRNA vaccines were only available in urban areas, while the BBIBP-CorV vaccine only required a standard cold chain, thus allowing a broader and faster immunization campaign in Peru [27]. Alternative technologies generated outside of the global north may continue to be important tools to prevent deaths in the global south while waiting for more effective vaccines to become widely available.

Some limitations of our study need to be addressed. First, as an observational study, the existence of residual confounding is possible. We addressed this issue adjusting for relevant known potentially confounding variables. In addition, there may be a risk of misclassification bias. This risk is low for all-cause mortality and COVID-19 mortality, due to the use of the SINADEF, which is the only registration system for all death certificates at the national level and which is considered to be highly accurate [28]. SARS-CoV-2 infection could have been underestimated due to the lack of access to COVID-19 diagnostic tests [23]. Finally, while we used nation-based datasets, the Peruvian information systems are not integrated, and missing data could be possible, but in a small proportion in outcomes variables.

To address the issue of missing data, we performed multiple imputation assuming missing at random data. We observed that the estimates of vaccine effectiveness for SARS-CoV-2 infection in the imputed models did not match the case-complete analysis model. On the other hand, estimates of vaccine effectiveness for the mortality outcomes were more homogenous. This incompatibility between models for infection effectiveness was unexpected, however, there are possible explanations for it, such as differential misclassification between certain groups or having data missing at random instead of only having data missing completely at random [20]. Therefore, our estimates of vaccine effectiveness on laboratory confirmed SARS-CoV-2 infection should be interpreted with caution. Finally, we cannot predict how our effectiveness estimates will vary with emergent SARS-CoV-2 variants or with waning immunity [29].

Although our study has some limitations, it remains relevant due to the limited information on the effectiveness of inactivated vaccines against COVID-19, also because the effects of the vaccine may differ depending on the population and the setting in which it is studied. To our knowledge, this is the first study of the real-world effect of the BBIBP-CorV vaccine in preventing death and infection in HCW and the study was carried out in a period in which lambda and gamma variants predominated in Peru. The results of our analysis could help build trust in the population by demonstrating that the vaccine worked, which could help combat misinformation.

5. Conclusion

The inactivated virus BBIBP-CorV vaccine showed high levels of effectiveness for preventing all-cause death and COVID-19 deaths in Peruvian HCW with complete immunization during a period on which variants with high infectivity rates and immune evasion were widely circulating in the country. These results were consistent within different subgroups and withstood sensitivity analyses.

Table 3
Effectiveness of the BBIBP-CorV vaccine in health workers ≥60 years of age related to all-cause mortality, COVID-19 mortality, and SARS-CoV-2 infection.

Outcomes	Person-days at risk	Outcome events	Outcome rate per 100,000 person-days[a]	Vaccine effectiveness[b] (95% CI)	
				Complete case analysis	Analysis with multiple imputation
All-cause Mortality					
Not immunized	4,796,168	476	9·92	..	..
Partially immunized	1,433,493	104	7·26	43·5 (40·7 to 59·3)	34·3 (17·7 to 47·5)
Fully immunized	4,437,557	100	2·25	89·3 (84·3 to 92·7)	79·2 (73·7 to 83·6)
COVID-19 Mortality					
Not immunized	4,796,168	310	6·46	..	..
Partially immunized	1,433,493	85	5·93	32·6 (30·8 to 64·9)	22·6 (−10·9 to 40·1)
Fully immunized	4,437,557	45	1·01	90·7 (92·1 to 97·5)	83·4 (76·8 to 88·1)
SARS-CoV-2 infection					
Not immunized	4,796,168	1990	41·49	..	..
Partially immunized	1,433,493	681	47·51	14·5 (5·6 to 22·5)	−4·3 (−13·7 to 4·3)
Fully immunized	4,437,557	1085	24·45	55·4 (51·5 to 58·9)	45·9 (41·8 to 49·8)

95% CI: 95% confidence interval.
[a] Outcome rate calculated for case complete analysis.
[b] Analyses adjusted for sex, macro-region, occupation, previous infection and the presence of obesity, diabetes, high blood pressure, cardiovascular disease, asthma or chronic pulmonary disease, and immunodeficiency or cancer.

Data sharing

Deidentified data can be made available by contacting the corresponding author following the information exchange policies of the INS Peru upon request.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Javier Silva-Valencia: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Percy Soto-Becerra:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Stefan Escobar-Agreda:** Formal analysis, Data curation, Visualization. **Manuel Fernandez-Navarro:** Writing – original draft, Visualization, Investigation. **Miguel Moscoso-Porras:** Methodology, Writing – original draft. **Lely Solari:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Percy Mayta-Tristán:** Writing – review & editing, Supervision.

Declaration of competing interest

We declare no competing interests.

Acknowledgments

We thank the MoH General Office of Information Technology team and the vaccination strategy implementation team for providing logistical assistance for this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2023.102565.

References

[1] World Health Organization. COVID-19 vaccine tracker and landscape. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. [Accessed 11 February 2022].
[2] Lancet T. COVID-19 in Latin America—emergency and opportunity. Lancet 2021;398:93.
[3] Wang H, Zhang Y, Huang B, et al. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. Cell 2020;182:713–21. e9.
[4] Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis 2021;21:39–51.
[5] Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: A Randomized Clinical Trial. Jama 2021;326(1):35–45.
[6] SAGE Working Group on COVID-19 vaccines. Evidence assessment: Sinopharm/BBIBP COVID-19 vaccine. World health organization. https://cdn.who.int/media/docs/default-source/immunization/sage/2021/april/2_sage29apr2021_critical-evidence_sinopharm.pdf; 2021.
[7] Argentina, Ministerio de Salud. Estudio efectividad de campaña nacional de vacunación en reducción de la mortalidad por COVID-19 en personas de 60 años y mayores. Argentina. vol. 17.
[8] Zhang X, Yu X, Wei D, et al. Neutralizing activity of BBIBP-CorV vaccine-elicited sera against multiple SARS-CoV-2 variants of concern. 2021. https://doi.org/10.21203/rs.3.rs-483022/v1. published online Aug 18.
[9] Wang G-L, Wang Z-Y, Duan L-J, et al. Susceptibility of circulating SARS-CoV-2 variants to neutralization. N Engl J Med 2021;384:2354–6.
[10] Jahromi M, Al Sheikh MH. Partial protection of Sinopharm vaccine against SARS COV2 during recent outbreak in Bahrain. Microb Pathog 2021 Sep;158:105086.
[11] Alhinai ZA, Elsidig N. Countries with similar COVID-19 vaccination rates yet divergent outcomes: are all vaccines created equal? Int J Infect Dis 2021;110:258–60.
[12] Karlinsky A, Kobak D. Tracking excess mortality across countries during the COVID-19 pandemic with the World Mortality Dataset. Elife 2021;10:e69336.
[13] Núñez-Zapata SF, Benites-Peralta B, Mayta-Tristan P, Rodríguez-Morales AJ. High seroprevalence for SARS-CoV-2 infection in South America, but still not enough for herd immunity! Int J Infect Dis 2021;109:244–6.
[14] Galán-Rodas E, Tarazona-Fernández A, Palacios-Celi M. Riesgo y muerte de los médicos a 100 días del estado de emergencia por el COVID-19 en Perú. Acta Méd Peru 2020;37:119–21.
[15] Escobar-Agreda S, Silva-Valencia J, Rojas-Mezarina L, Vargas-Herrera J. Supervivencia de los trabajadores de salud infectados por SARS-CoV-2 en el contexto de la vacunación contra la COVID-19 en el Perú. An Fac Med 2021;82. https://doi.org/10.15381/anales.v82i2.20766.
[16] Padilla-Rojas C, Jimenez-Vasquez V, Hurtado V, et al. Genomic analysis reveals a rapid spread and predominance of lambda (C.37) SARS-COV-2 lineage in Peru despite circulation of variants of concern. J Med Virol; n/a. DOI:10.1002/jmv.27261.
[17] Dirección General de Medicamentos, Insumos y Drogas-DIGEMID. Ficha técnica - Vacuna contra el COVID-19 (Vero cell), Inactivada. https://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/COVID19/VACUNAS/SINOPHARM_RD-12217-2021/FICHA_TECNICA.PDF; 2021.
[18] Vargas-Herrera J, Segovia-Juarez J. Garro Nuñez GM. Sistema de información de la red nacional de laboratorios de salud pública en el Perú (Netlab). Rev Peru Med Exp Salud Pública 2015;32:378–84.
[19] Nandy K, Salunke A, Pathak SK, et al. Coronavirus disease (COVID-19): a systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. Diabetes Metabol Syndr 2020;14:1017–25.
[20] Van Buuren S. Second edition. In: Flexible imputation of missing data. second ed. | Boca Raton, Florida: CRC Press; 2018 [2019] |: Chapman and Hall/CRC.
[21] World Health Organization. Weekly epidemiological update on COVID-19-15 June 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—15-june-2021. [Accessed 9 August 2021].
[22] Baj A, Novazzi F, Ferrante FD, et al. Introduction of SARS-COV-2 C.37 (WHO VOI lambda) from Peru to Italy. J. Med. Virol.; n/a. DOI:10.1002/jmv.27235.
[23] Louca S. SARS-CoV-2 infections in 165 countries over time. Int J Infect Dis 2021. https://doi.org/10.1016/j.ijid.2021.08.067. 0.
[24] Trogen B, Caplan A. Risk compensation and COVID-19 vaccines. Ann Intern Med 2021:M20–8251.
[25] Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 2021;397:1819–29.
[26] Waning immunity of the BNT162b2 vaccine. A nationwide study from Israel | medRxiv. https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1. [Accessed 11 February 2022].
[27] Paltiel AD, Zheng A, Schwartz JL. Speed versus efficacy: quantifying potential tradeoffs in COVID-19 vaccine deployment. Ann Intern Med 2021;174:568–70.
[28] Vargas-Herrera J, Pardo Ruiz K, Garro Nuñez G, et al. Resultados preliminares del fortalecimiento del sistema informático nacional de defunciones. Rev Peru Med Exp Salud Pública 2018;35:505–14.
[29] Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021 May 13;373:n1088.